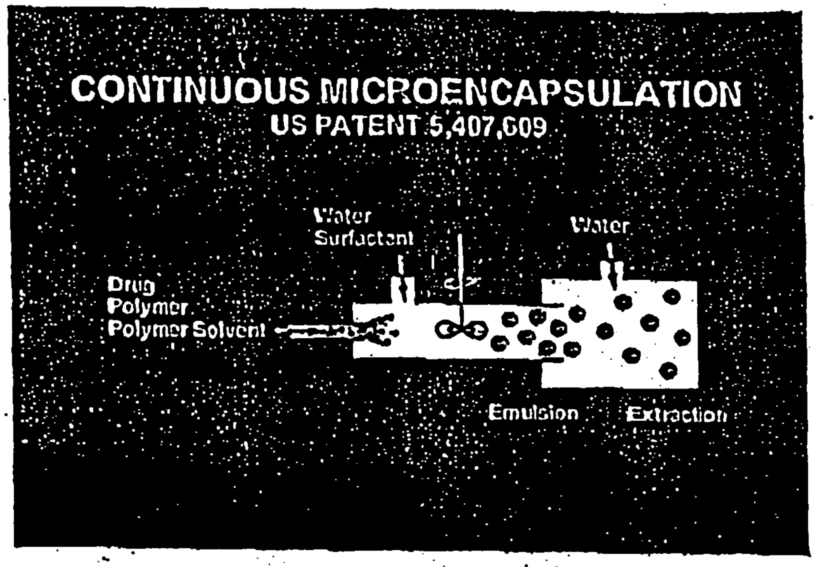
SOUTHERN RESEARCH'S PATENTED MICROENCAPSULATION PROCESS



Advantages

- US Patent issued 1995
- Fast encapsulation time -- milliseconds
- Minimal exposure to polymer solvent
- High encapsulation efficiency
- Good Yields
- Makes small microparticles
  <100 micron <10 micron

Drugs Microencapsulated

- Proteins
- Peptides
- Small molecules
- Water-soluble drugs
- Hydrophobic drugs
- Drugs encapsulated in
  lactide/glycolide polymers

FIGURE 1

FIGURE 2

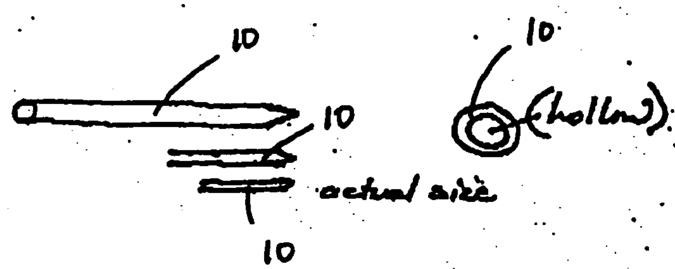
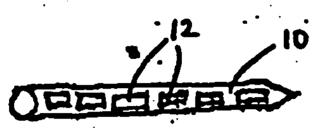


FIGURE 3



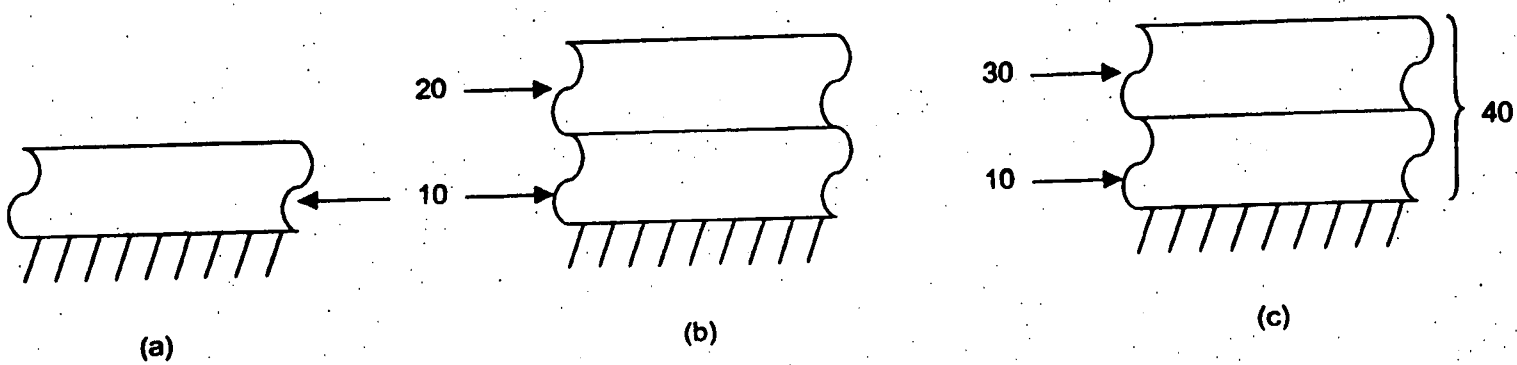


FIGURE 4

Conditions: Ambient

Material:	PX510	PX261	PX749	PX125	PX510 + 14% Paclitaxel
Hardness:	F	B	3B	4B	F

Conditions: 5 minutes in 37°C pH 7.4 Saline Buffer

Material:	PX510	PX261	PX749	PX125	PX510 + 14% Paclitaxel
Hardness:	F	B	9B	<9B	F

Hardness Rating: 2H-H-F-HB-B-2B-3B-4B-5B-6B-7B-8B-9B

Harder ⟷ Softer

FIGURE 5

Conditions: Ambient

Material:	PX510	PX261	PX749	PX125	PX510 + 14% Paclitaxel
Resistance To Cracking	< 3 mm	< 3 mm	< 3mm	< 3mm	<3mm

Conditions: 5 minutes in 37°C pH 7.4 Saline Buffer

Material:	PX510	PX261	PX749	PX125	PX510 + 14% Paclitaxel
Resistance To Cracking	< 3 mm	< 3 mm	< 3mm	< 3mm	< 3mm

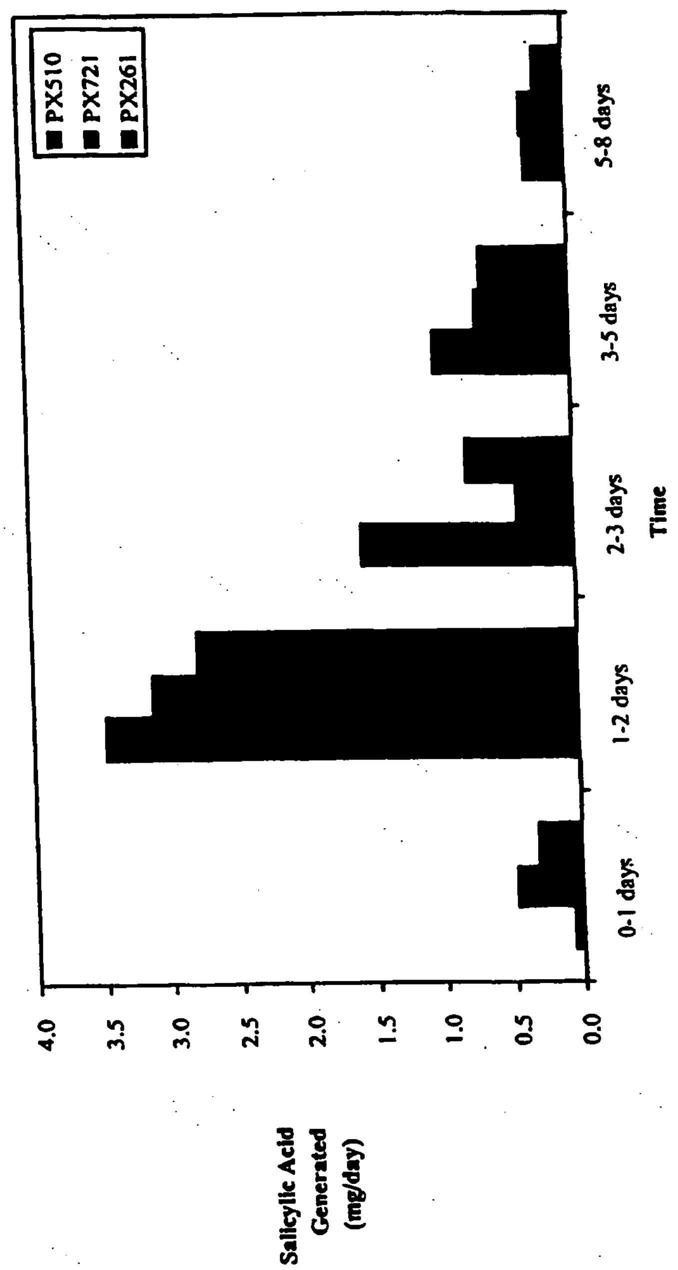
FIGURE 6

Conditions: Ambient

Material:	PX510	PX261	PX749	PX125	PX510 + 14% Paclitaxel
Class:	5B	5B	5B	4B	5B

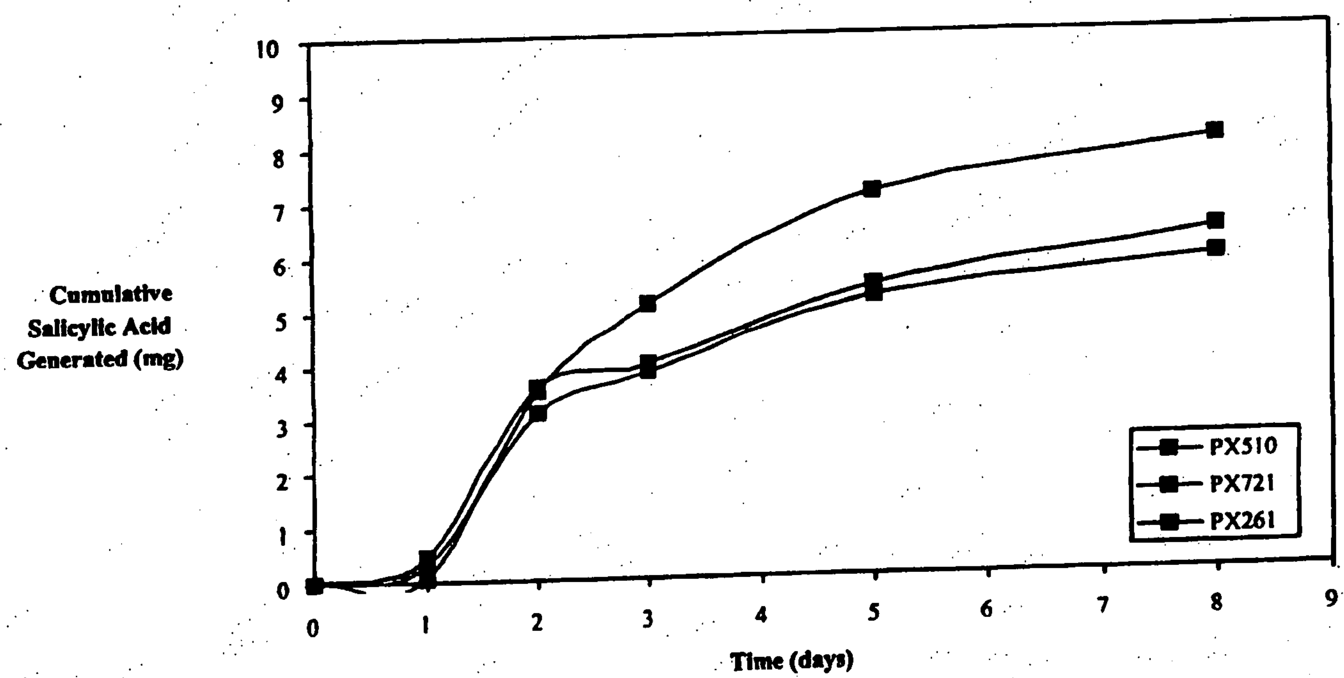
Class Rating: 5B = 0% of coating removed from substrate
4B = Less than 5% of coating removed from substrate

FIGURE 7



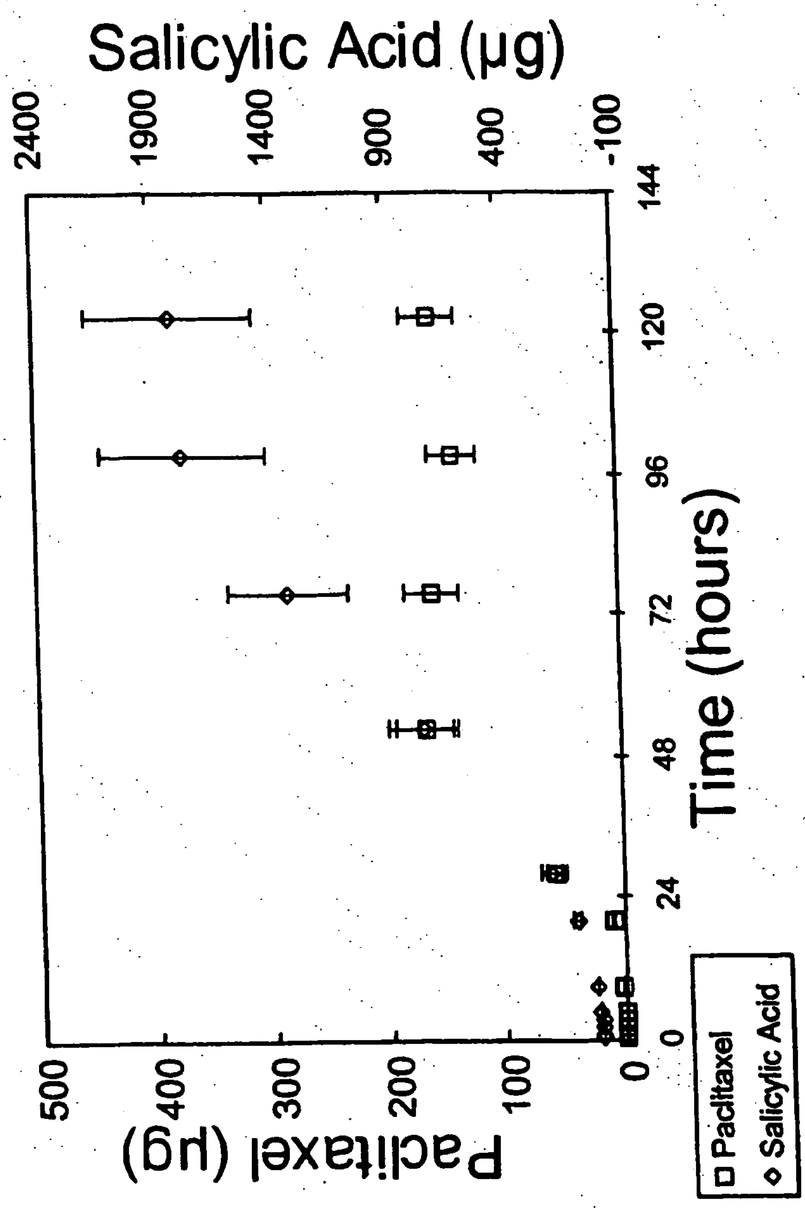
PX510
PX721
PX261
Salicylic Acid Generated (mg/day)
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0-1 days
1-2 days
2-3 days
3-5 days
5-8 days
Time

FIGURE 8A



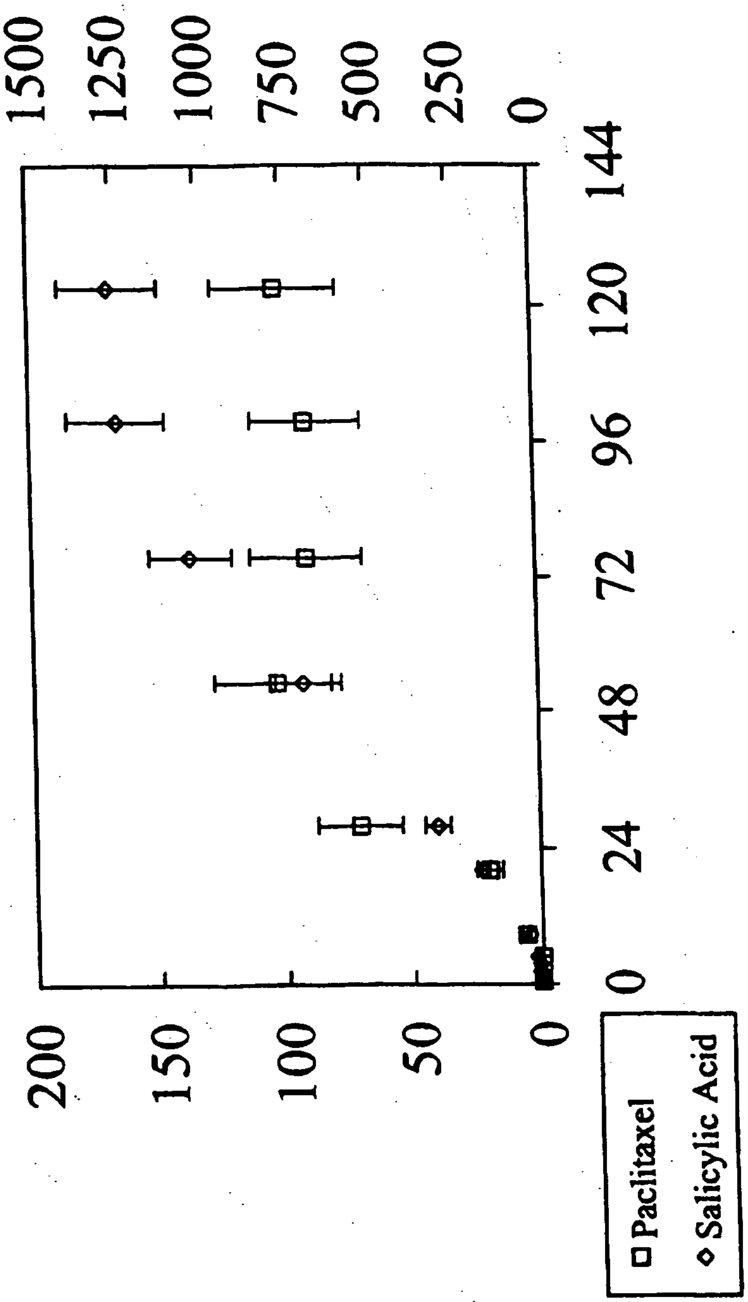
Cumulative Salicylic Acid Generated (mg)
Time (days)
PX510
PX721
PX261
0
1
2
3
4
5
6
7
8
9
10

FIGURE 8B



Salicylic Acid (µg)
2400
1900
1400
900
400
-100
500
400
300
200
100
0
Paclitaxel (µg)
0
24
48
72
96
120
144
Time (hours)
Paclitaxel
Salicylic Acid

FIGURE 9A



Paclitaxel
Salicylic Acid
0
50
100
150
200
0
250
500
750
1000
1250
1500
0
24
48
72
96
120
144

FIGURE 9B

Property	Formulation			
	PX510	PX721	PX261	PX749
T_g (C)	44	38	29	16
Tensile modulus (MPa)	2.0 (25 C) 5.1 (37 C)			3.0 (25 C)
Yield Strength (MPa)	Not observed			6.0 (25 C)
Ultimate Elongation (%)	1.5 (25 C) 350 (37 C)			500 (25 C)

FIGURE 10

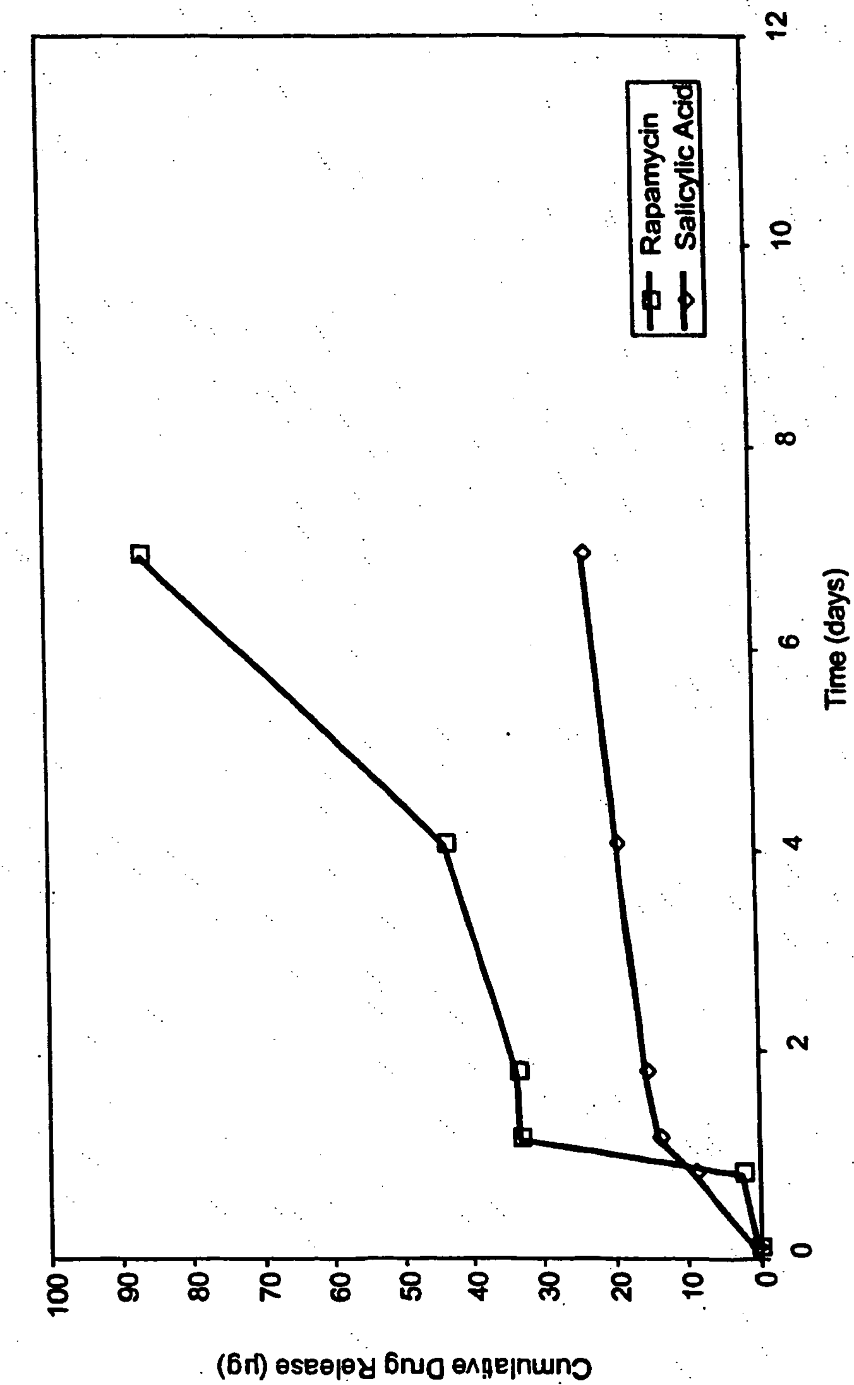

Cumulative Drug Release (µg)
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
Time (days)
Rapamycin
Salicylic Acid

FIGURE 11

Property	E Beam (3 MRad)			γ (25-35 KGys)		
	PX510	PX721	PX261	PX510	PX721	PX261
MW	-28%	-39%	-26%	-14%	N/C	N/C
Hardness	-2 units	N/C	-1 unit	N/C	-3 units	-2 units
Flexibility	N/C	N/C	N/C	N/C	N/C	N/C
Adhesion	N/C	N/C	-1 unit	N/C	N/C	N/C

N/C: no change

FIGURE 12

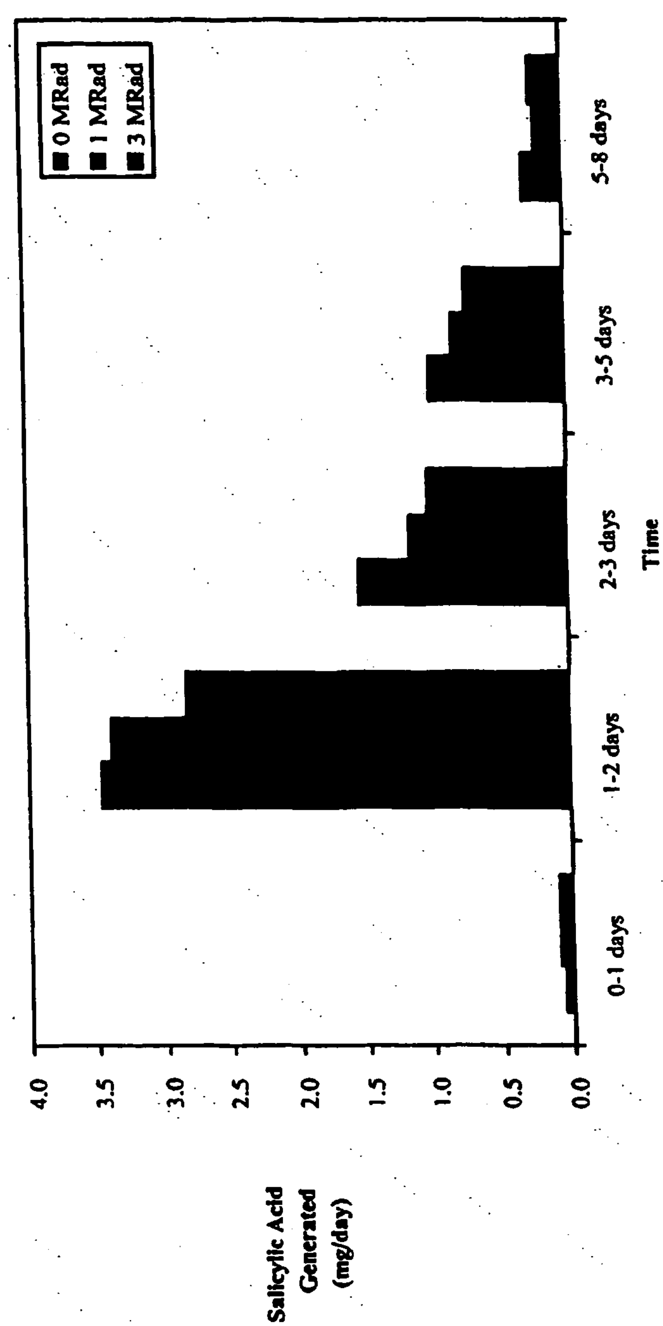
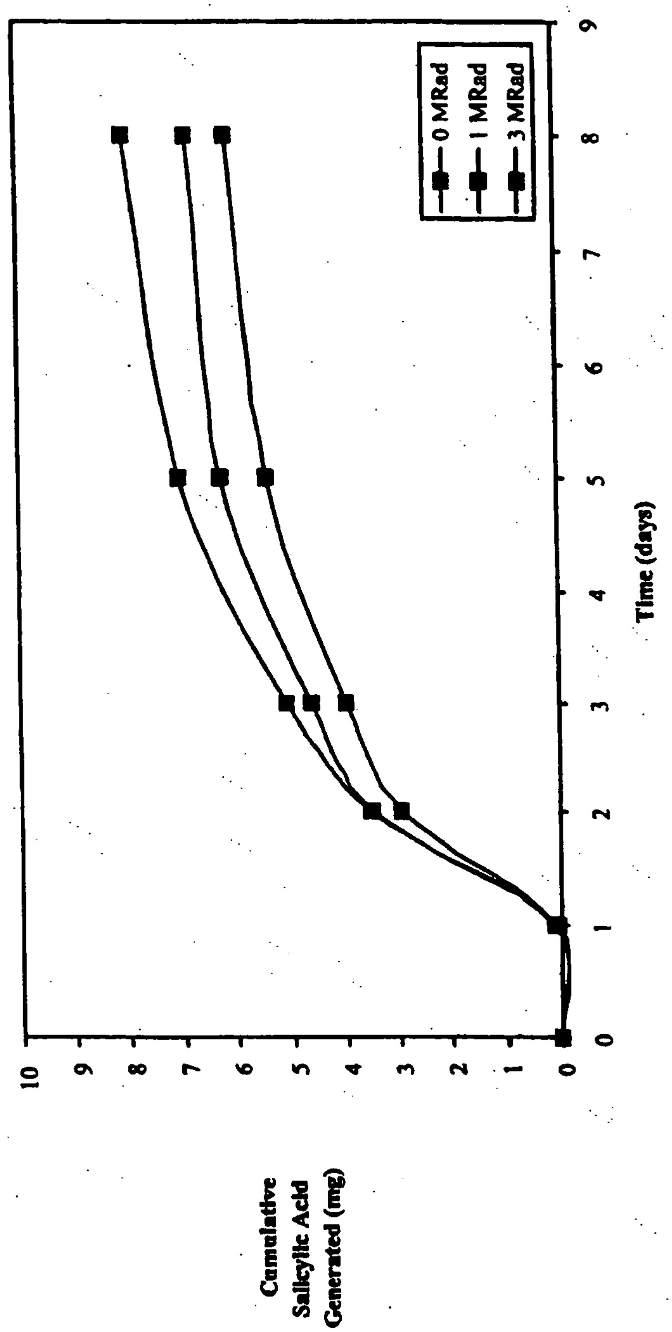

0 MRad
1 MRad
3 MRad
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0-1 days
1-2 days
2-3 days
3-5 days
5-8 days
Time
Salicylic Acid Generated (mg/day)

FIGURE 13A



0 MRad
1 MRad
3 MRad
Cumulative Salicylic Acid Generated (mg)
Time (days)
0
1
2
3
4
5
6
7
8
9
10

FIGURE 13B

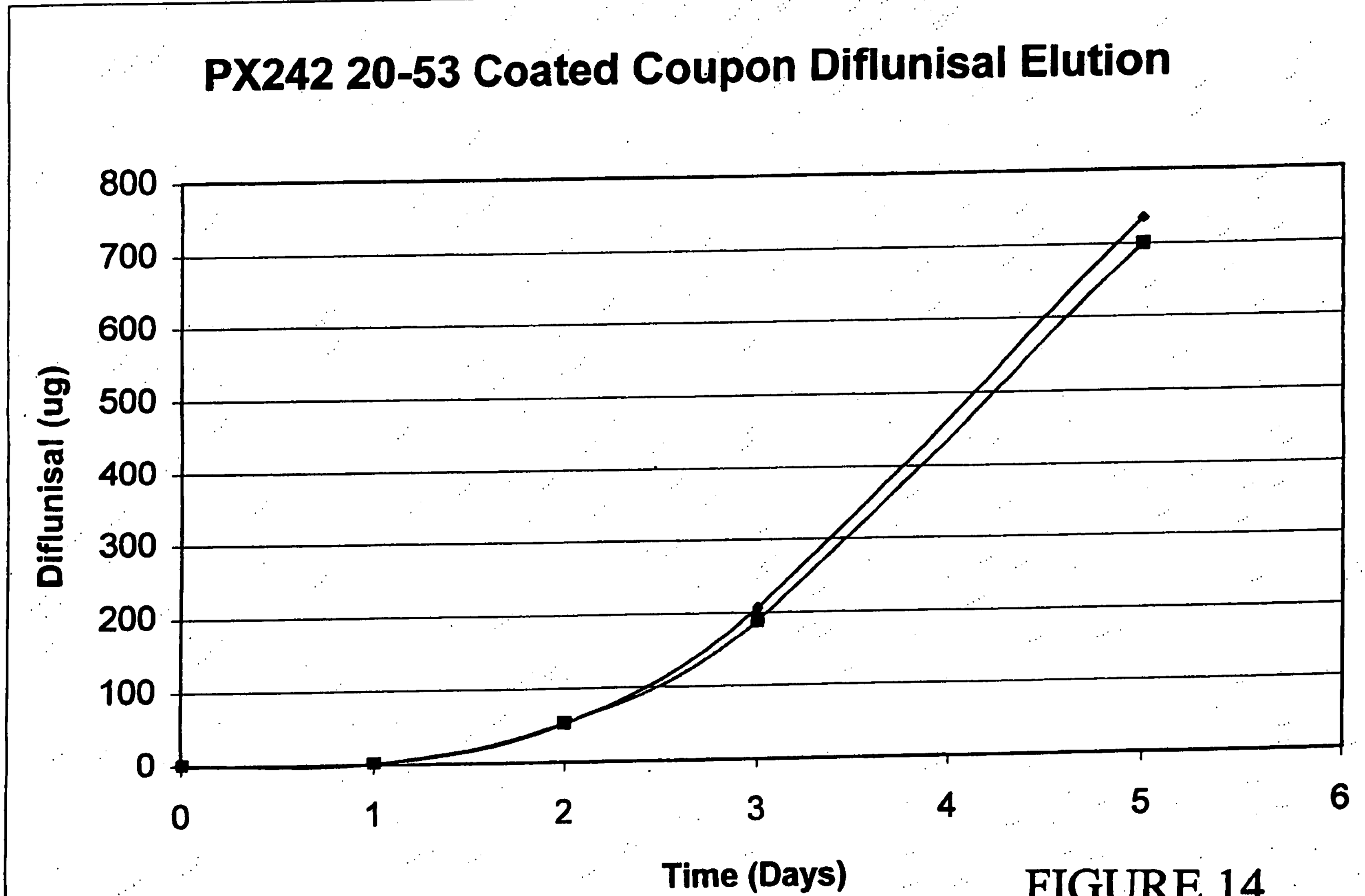

PX242 20-53 Coated Coupon Diflunisal Elution
Diflunisal (ug)
800
700
600
500
400
300
200
100
0
0
1
2
3
4
5
6
Time (Days)

FIGURE 14

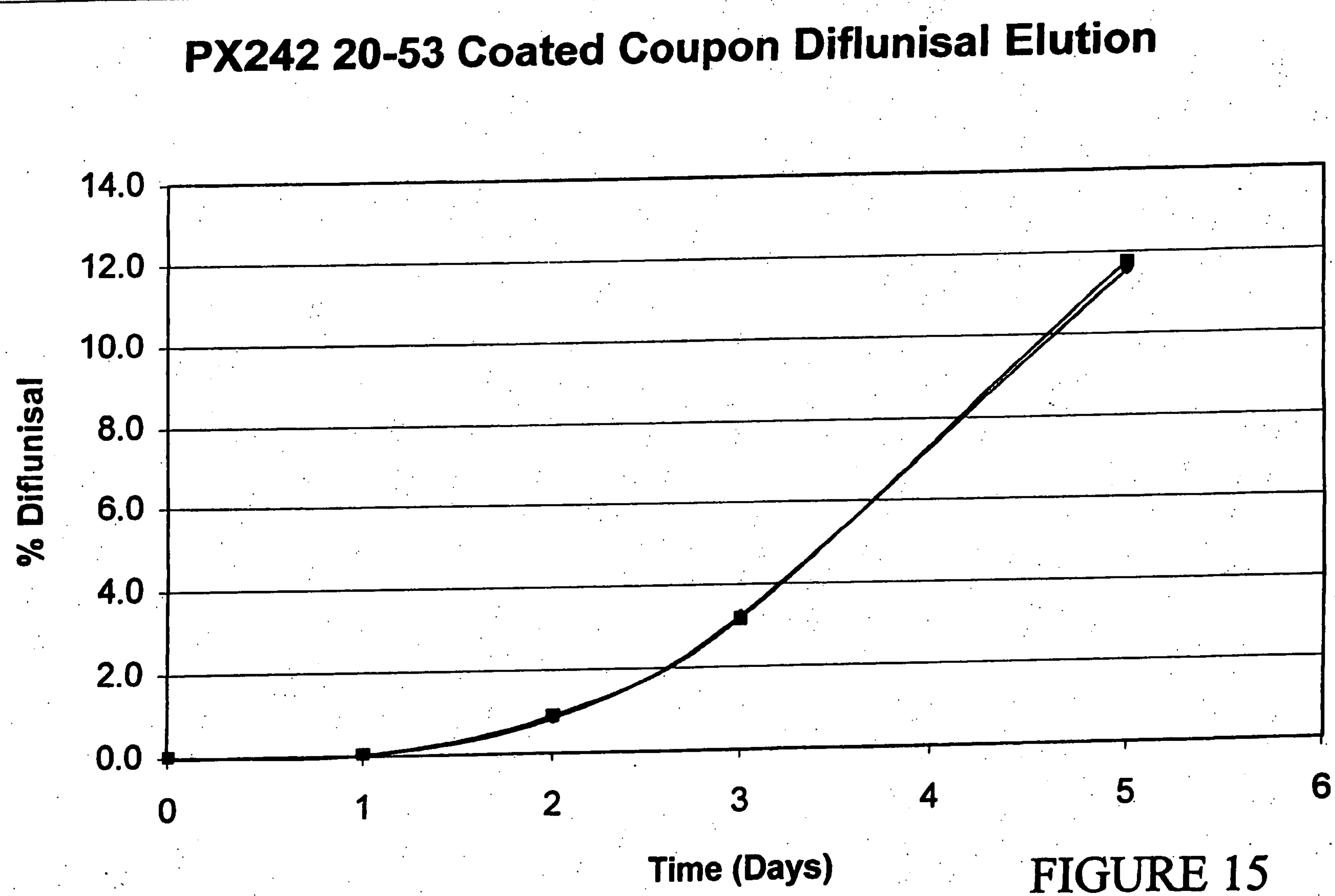

PX242 20-53 Coated Coupon Diflunisal Elution
% Diflunisal
14.0
12.0
10.0
8.0
6.0
4.0
2.0
0.0
0
1
2
3
4
5
6
Time (Days)

FIGURE 15

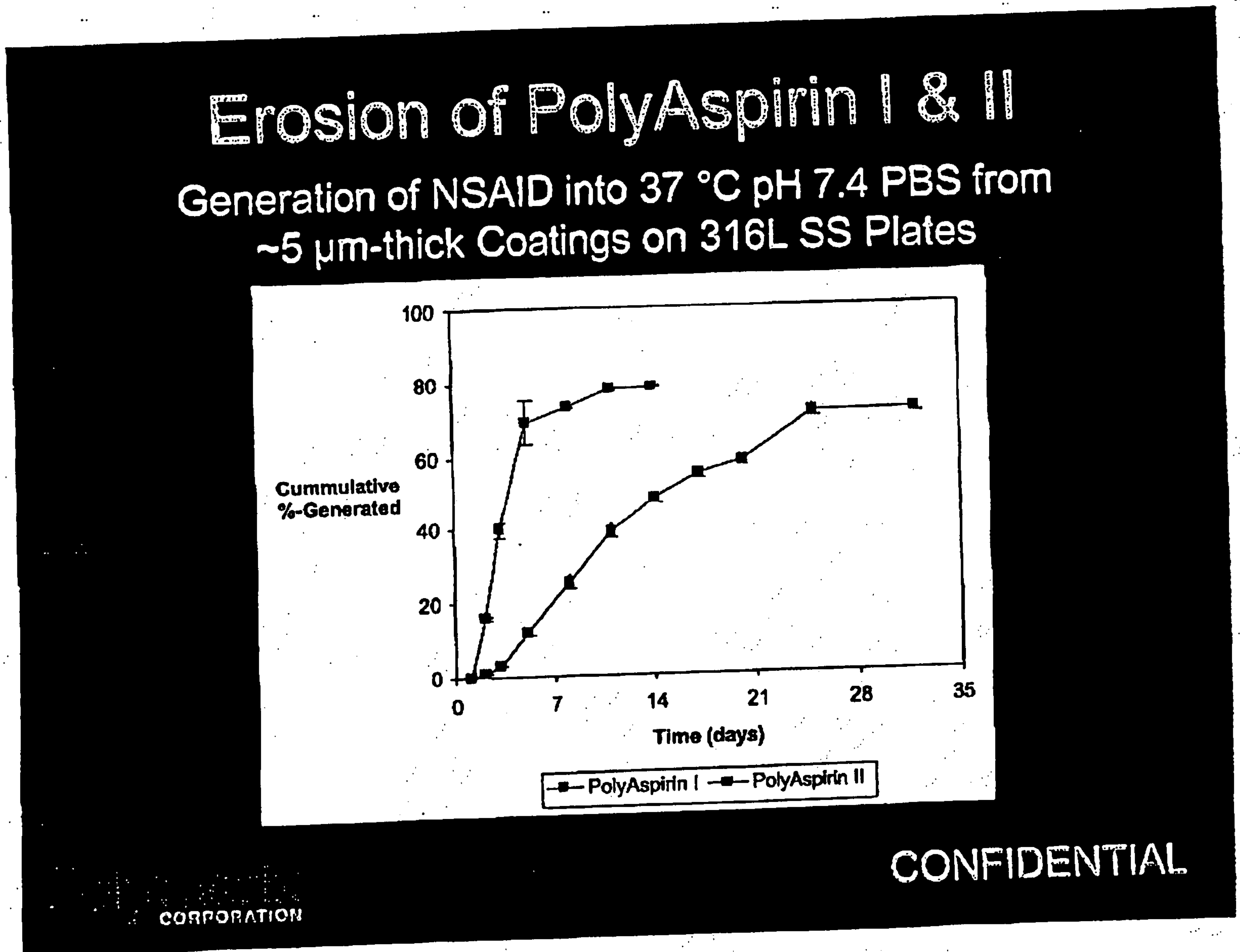

Erosion of PolyAspirin I & II
Generation of NSAID into 37 °C pH 7.4 PBS from ~5 μm-thick Coatings on 316L SS Plates
Cummulative %-Generated
100
80
60
40
20
0
0
7
14
21
28
35
Time (days)
PolyAspirin I
PolyAspirin II
CONFIDENTIAL
CORPORATION

FIG. 16

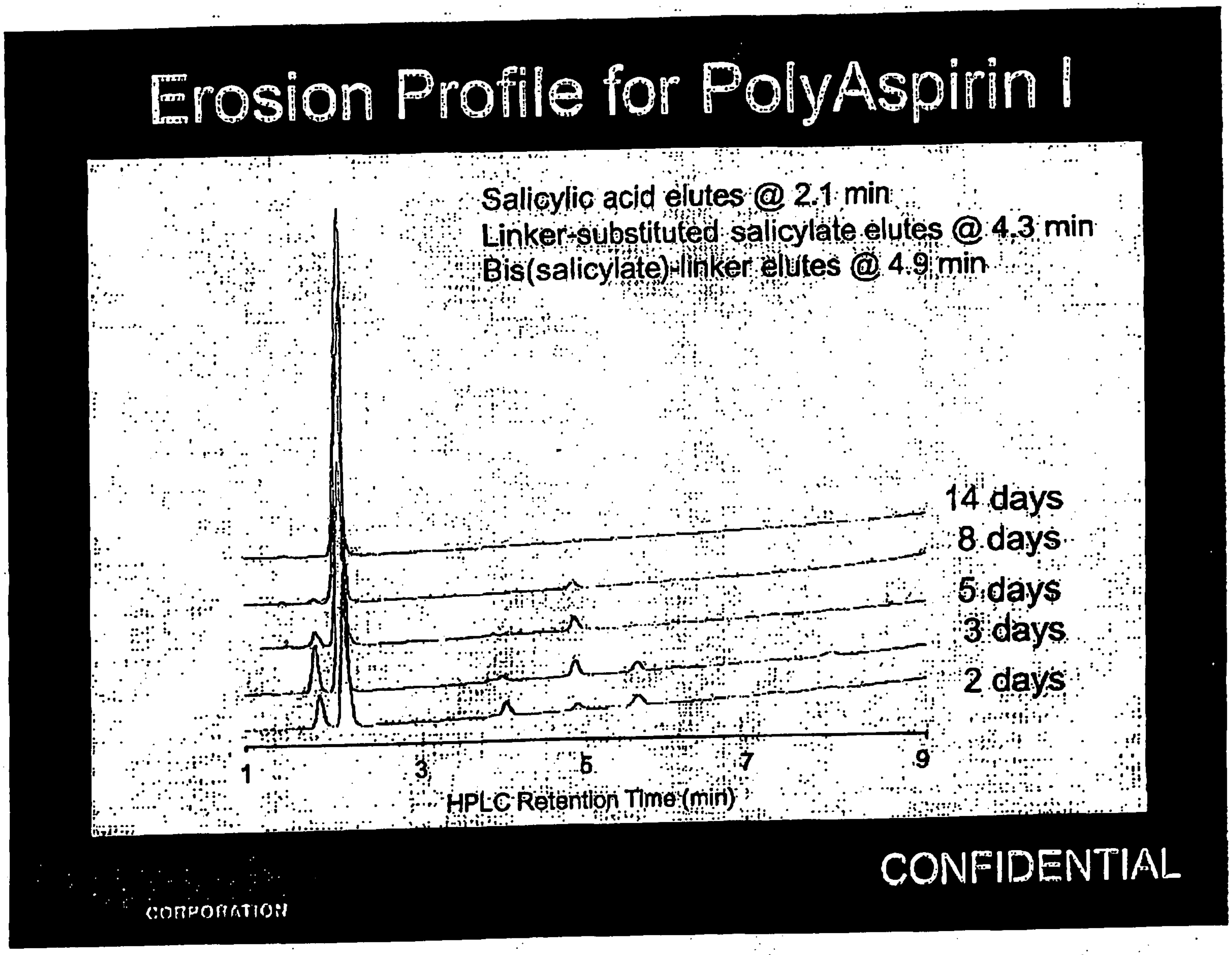

Erosion Profile for PolyAspirin I
Salicylic acid elutes @ 2.1 min
Linker-substituted salicylate elutes @ 4.3 min
Bis(salicylate)-linker elutes @ 4.9 min
14 days
8 days
5 days
3 days
2 days
1
3
5
7
9
HPLC Retention Time (min)
CONFIDENTIAL
CORPORATION

FIG. 17

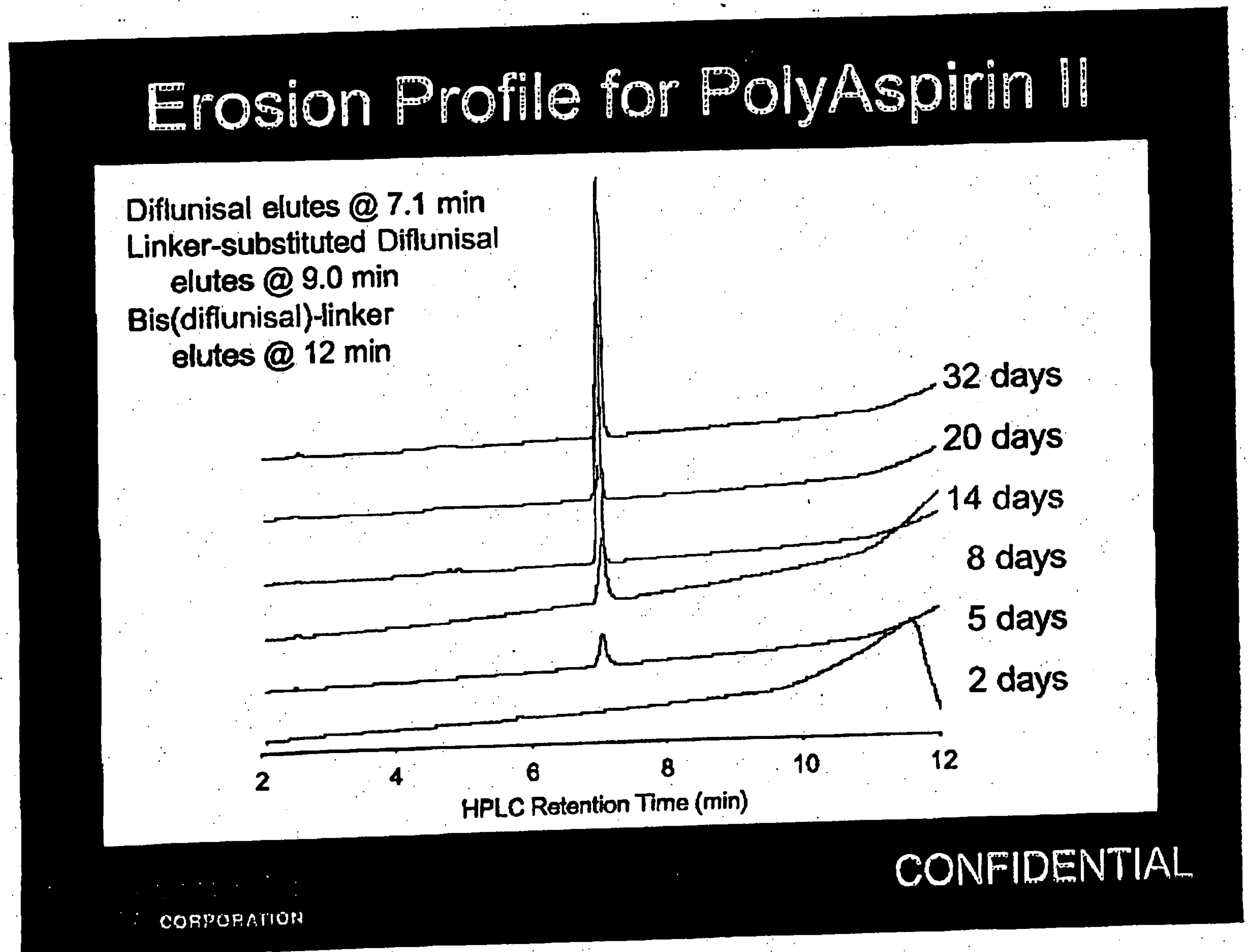

Erosion Profile for PolyAspirin II
Diflunisal elutes @ 7.1 min
Linker-substituted Diflunisal elutes @ 9.0 min
Bis(diflunisal)-linker elutes @ 12 min
32 days
20 days
14 days
8 days
5 days
2 days
2
4
6
8
10
12
HPLC Retention Time (min)
CONFIDENTIAL
CORPORATION

FIG. 18

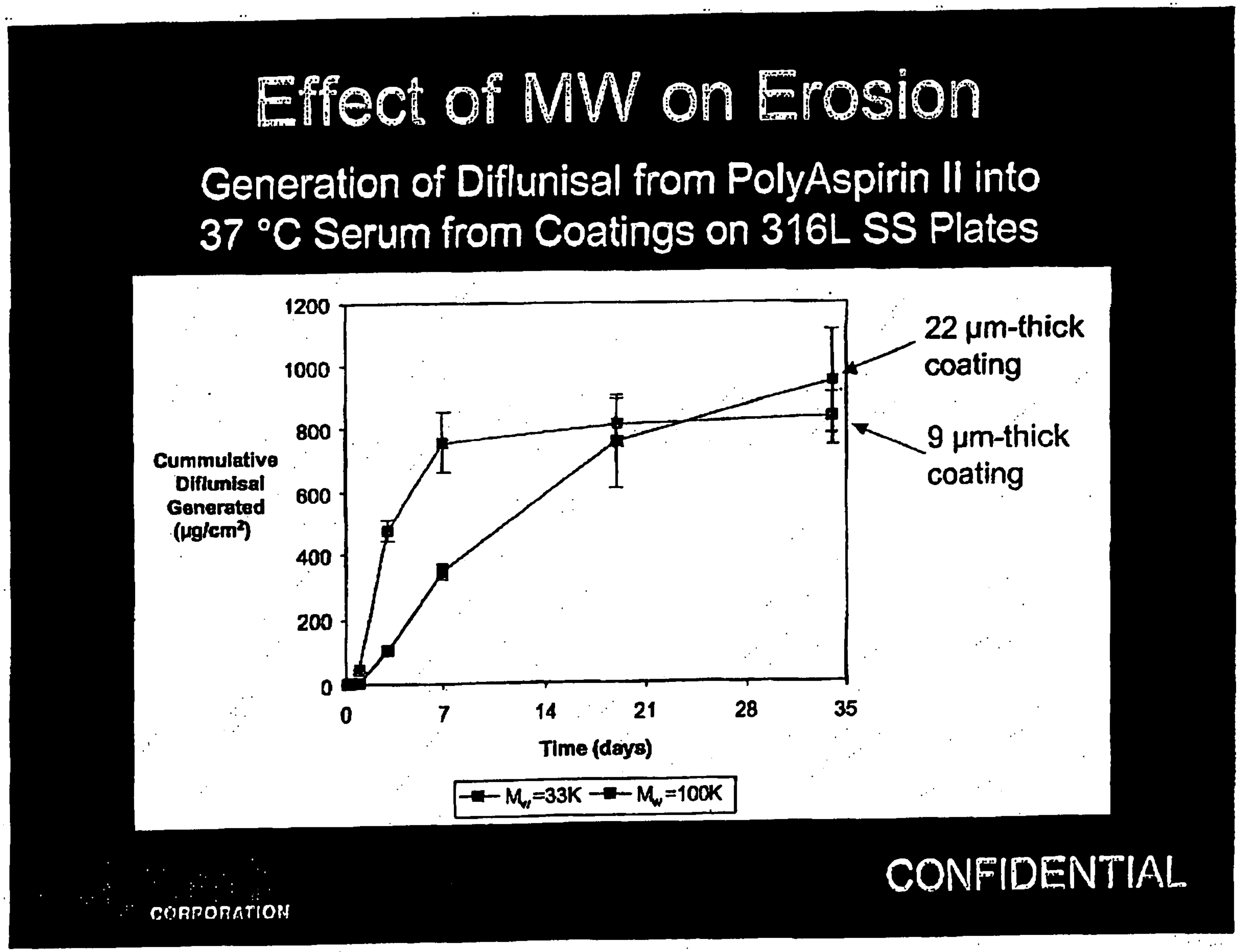
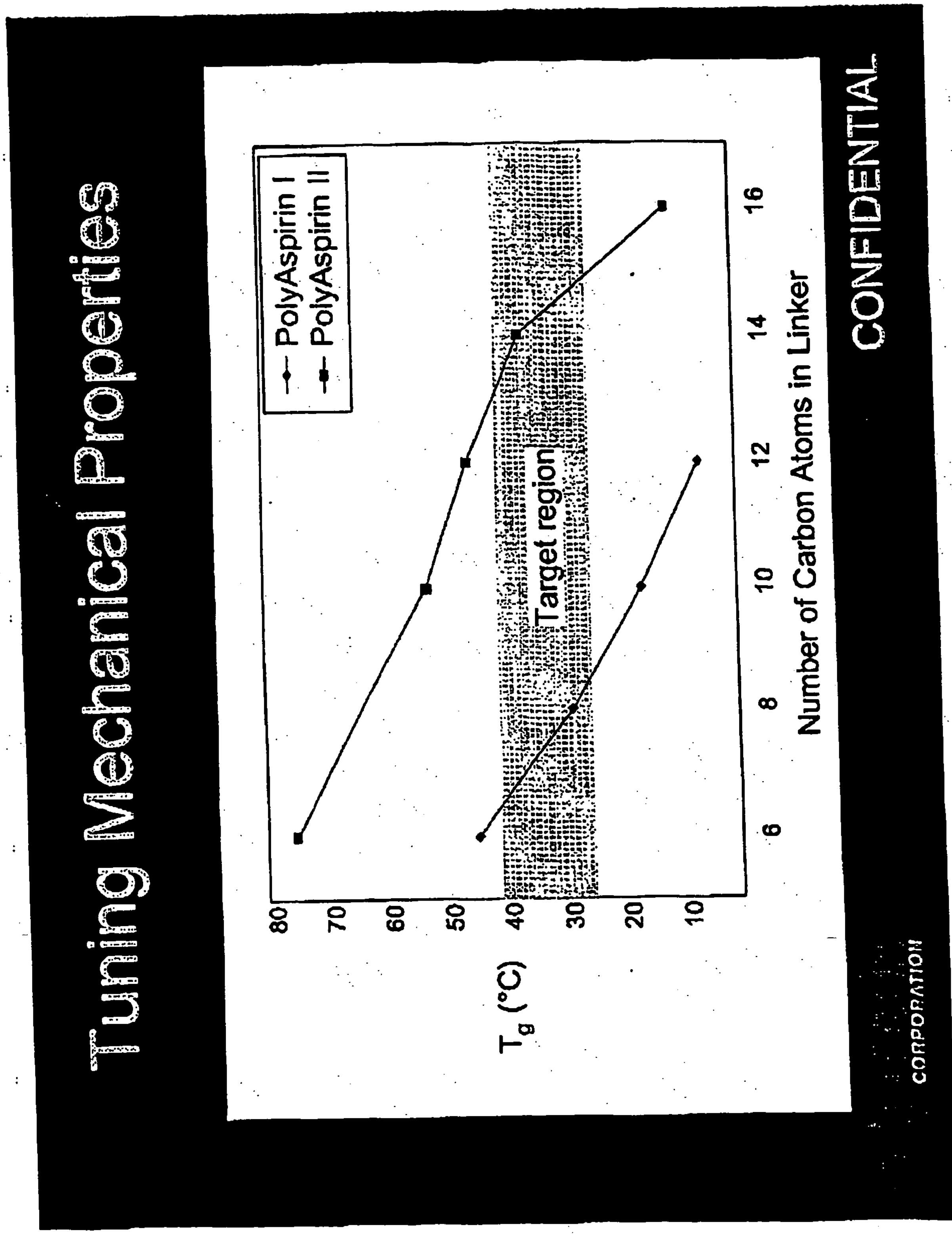

Effect of MW on Erosion
Generation of Diflunisal from PolyAspirin II into
37 °C Serum from Coatings on 316L SS Plates
Cummulative Diflunisal Generated (μg/cm²)
1200
1000
800
600
400
200
0
0
7
14
21
28
35
Time (days)
22 μm-thick coating
9 μm-thick coating
Mw=33K
Mw=100K
CONFIDENTIAL
CORPORATION

FIG. 19



Tuning Mechanical Properties
PolyAspirin I
PolyAspirin II
Target region
Tg (°C)
80
70
60
50
40
30
20
10
6
8
10
12
14
16
Number of Carbon Atoms in Linker
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FIG. 20

Thermoanalysis of PolyAspirin™

Property	PolyAspirin I	PolyAspirin II	
	PX261	PX657	
	$M_w \sim 20K$	$M_w \sim 33K$	$M_w \sim 100K$
T_g (°C)	29	36	44
Ultimate Stress (kPa)	1700 (25°C) >2000 (37°C)	>2800 (25°C)	>2600 (25°C)
Ultimate Elongation (%)	>500 (25°C) >500 (37°C)	>4 (25°C)	>500 (25°C)
Toughness (kPa)	>3900 (25°C) >4400 (37°C)	>560 (25°C)	>4000 (25°C)

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FIG. 21

Properties of PolyAspirin™ Coatings

Test	PolyAspirin I PX261 M_w ~ 20K	PolyAspirin II PX657 M_w ~ 33K	PolyAspirin II PX657 M_w ~ 100K
Hardness			
Ambient	B	F	3H
5 min in PBS, 37 °C	B	2B	B
1 hr in PBS, 37 °C	-	8B	4B
Flexibility			
Ambient	<3 mm	<3 mm	<3 mm
5 min in PBS, 37 °C	<3 mm	<3 mm	<3 mm
1 hr in PBS, 37 °C	-	<3 mm	<3 mm
Adhesion			
Ambient	5B	5B	5B

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FIG. 22

PolyAspirin Coatings with Admixtures

Test	PolyAspirin II (PX657) No Admixture	PolyAspirin II (PX657) 20% Paclitaxel Admixed
Hardness		
Ambient	F	F
5 min in PBS, 37 °C	2B	F
1 hr in PBS, 37 °C	8B	6B
Flexibility		
Ambient	<3 mm	<3 mm
5 min in PBS, 37 °C	<3 mm	<3 mm
1 hr in PBS, 37 °C	<3 mm	<3 mm
Adhesion		
Ambient	5B	5B

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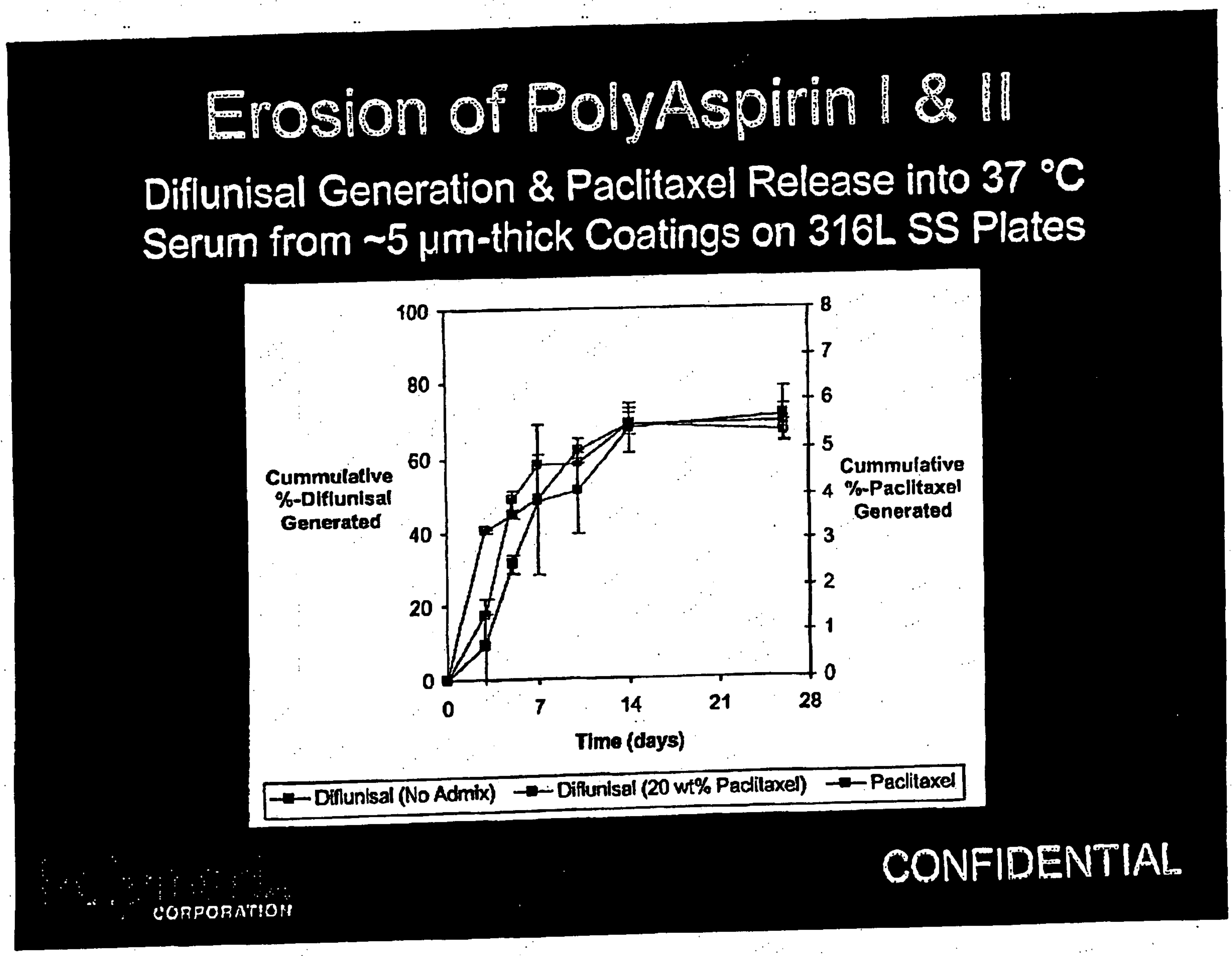
FIG. 23



Erosion of PolyAspirin I & II
Diflunisal Generation & Paclitaxel Release into 37 °C Serum from ~5 μm-thick Coatings on 316L SS Plates
Cummulative %-Diflunisal Generated
100
80
60
40
20
0
8
7
6
5
4
3
2
1
0
Cummulative %-Paclitaxel Generated
0
7
14
21
28
Time (days)
Diflunisal (No Admix)
Diflunisal (20 wt% Paclitaxel)
Paclitaxel
CONFIDENTIAL
CORPORATION

FIG. 24

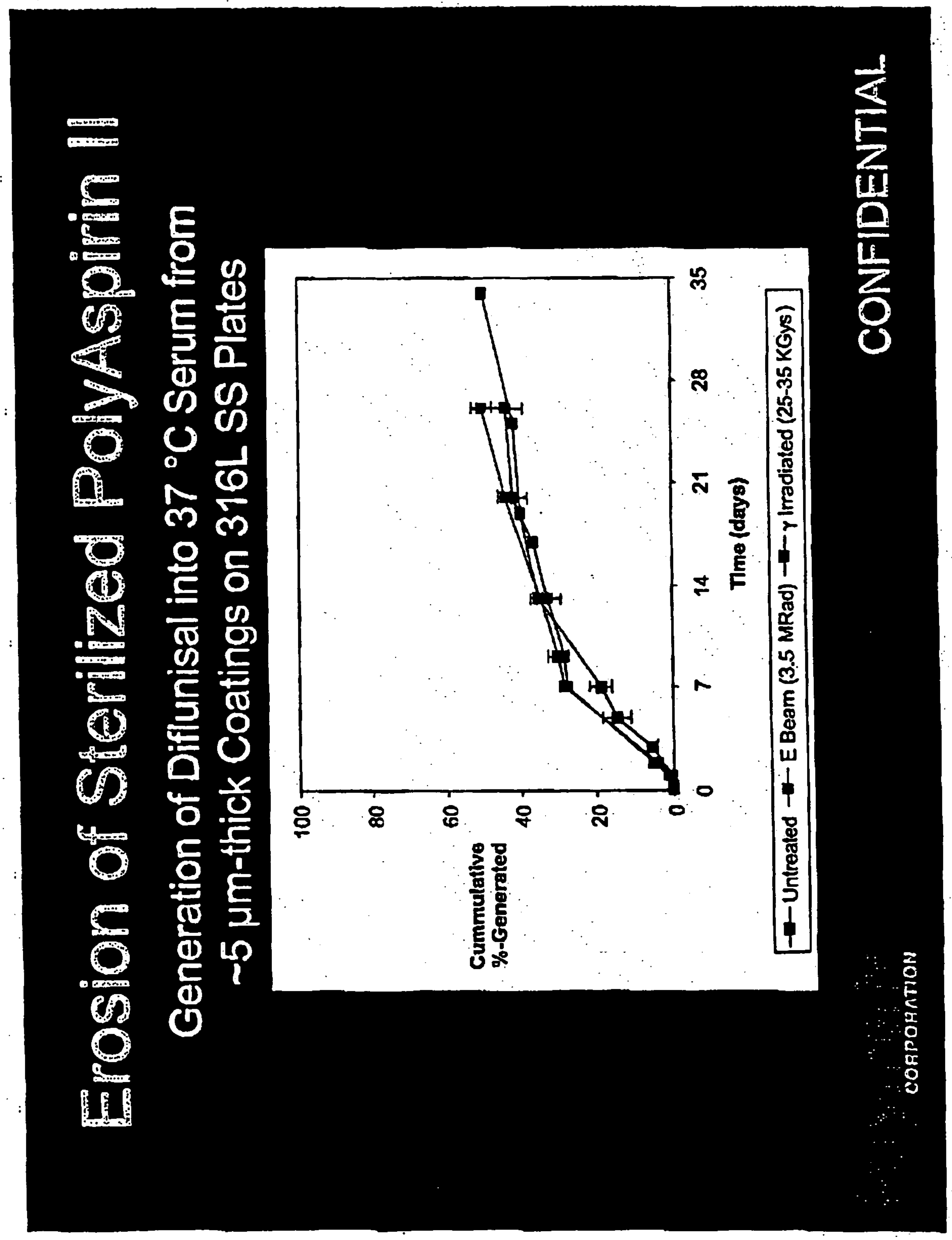

Erosion of Sterilized PolyAspirin II
Generation of Diflunisal into 37 °C Serum from
~5 µm-thick Coatings on 316L SS Plates
Cummulative
%-Generated
100
80
60
40
20
0
0
7
14
21
28
35
Time (days)
Untreated
E Beam (3.5 MRad)
γ Irradiated (25-35 KGys)
CORPORATION
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FIG. 25

γ Irradiation (25-35 Kgys)

Property	PolyAspirin I PX261 $M_w \sim 20K$	PolyAspirin II PX657 $M_w \sim 100K$
MW	N/C	-50%
Hardness	-2 units	-3 units
Flexibility	N/C	-
Adhesion	N/C	-

N/C: no change

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FIG. 26

E Beam (3-4.5 MRad)

Property	PolyAspirin I	PolyAspirin II	
	PX261	PX657	
	$M_w \sim 20$ K	$M_w \sim 33$K	$M_w \sim 80$K
MW	-26%	+5%	-30%
Hardness	-1 unit	+2 units	N/C
Flexibility	N/C	-	N/C
Adhesion	-1 unit	-	-

N/C: no change

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FIG. 27

Kinetics of NSAID Generation

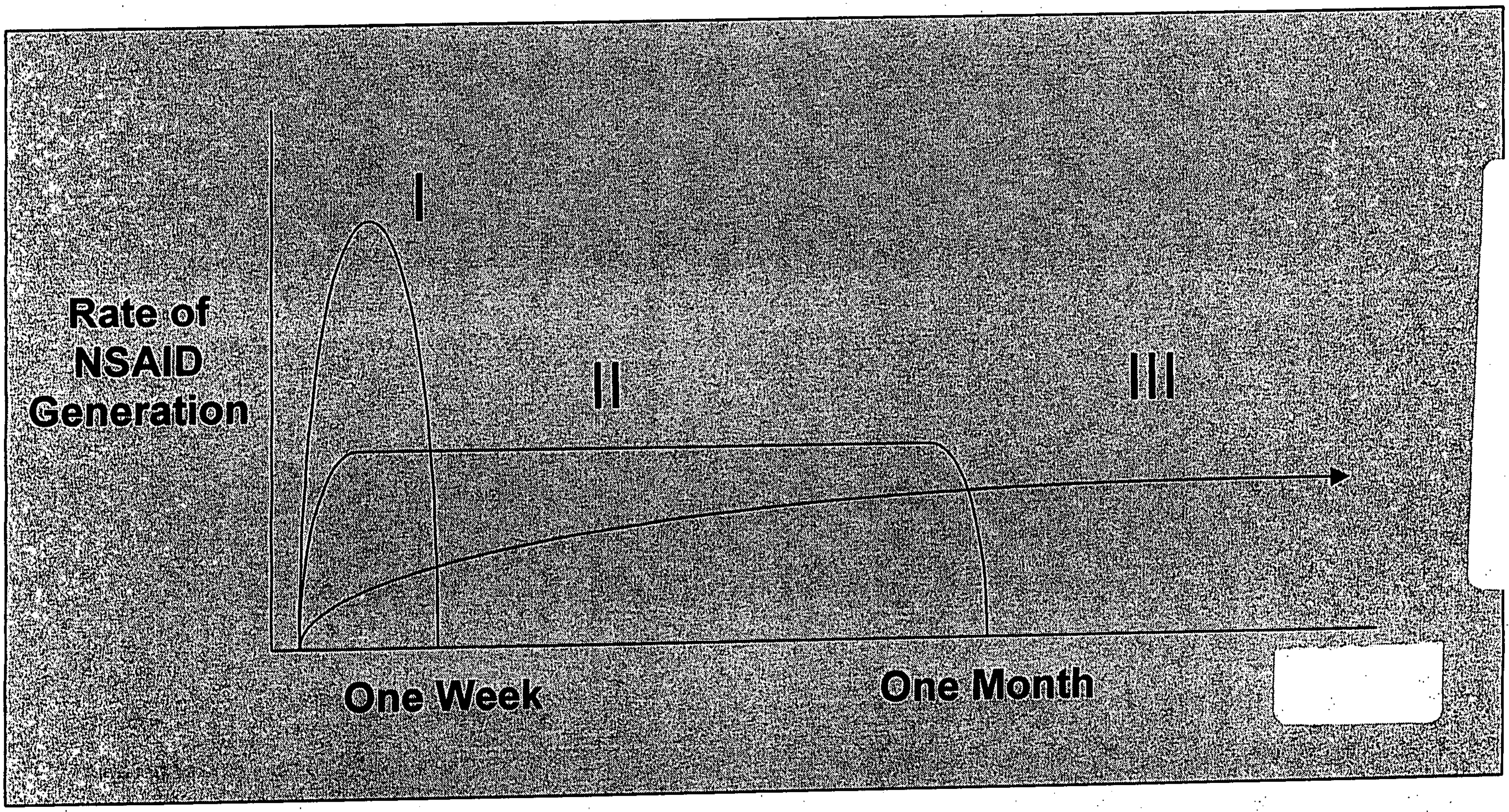


FIG. 28

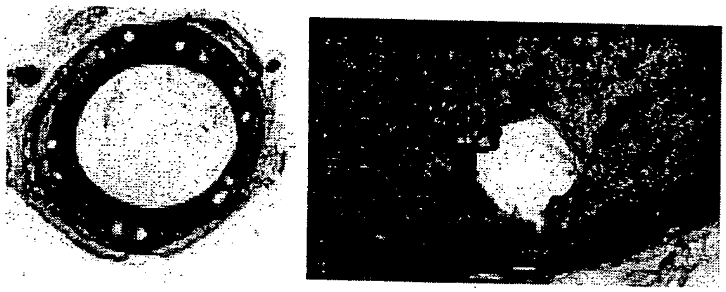


FIG. 29

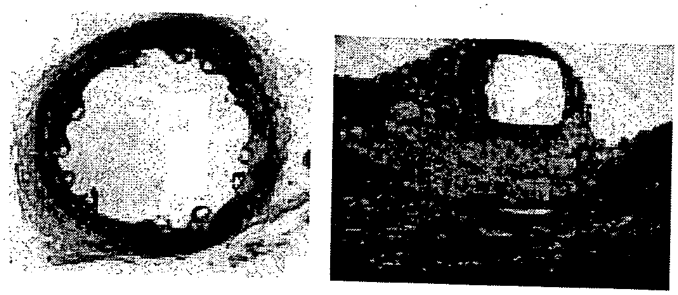


FIG. 30

FIG. 31

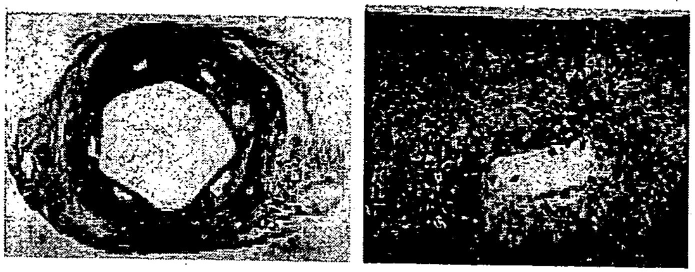


FIG. 32

FIG. 33

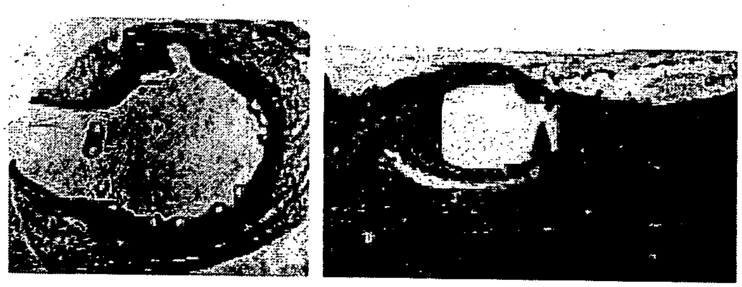


FIG. 34

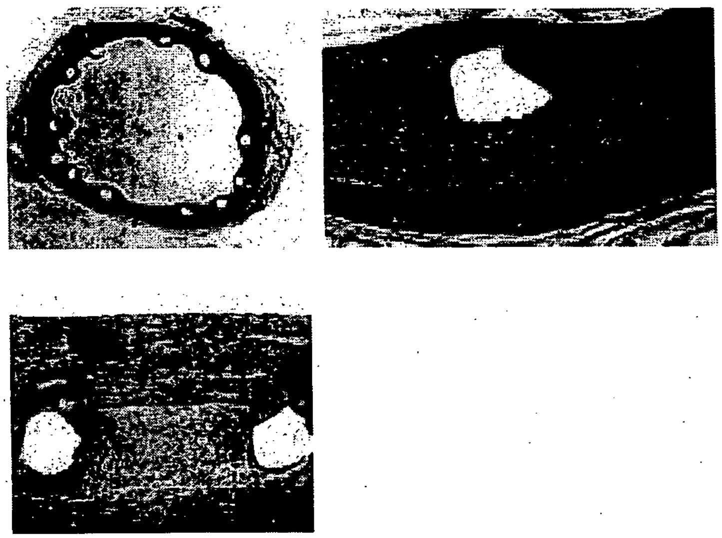


FIG. 35

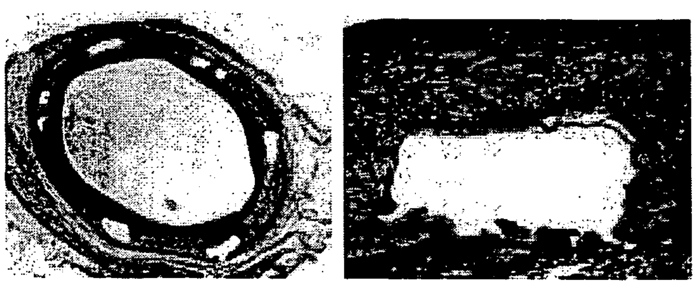


FIG. 36

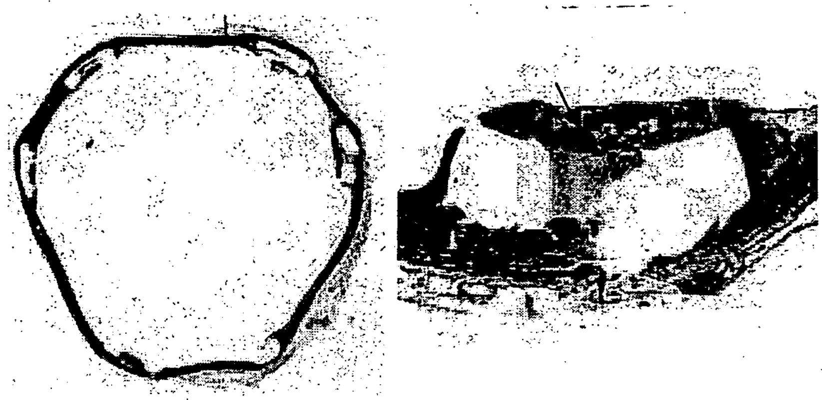


FIG. 37

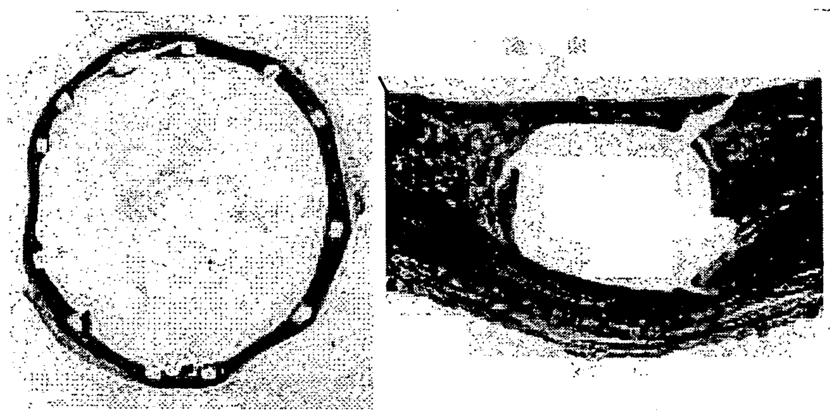
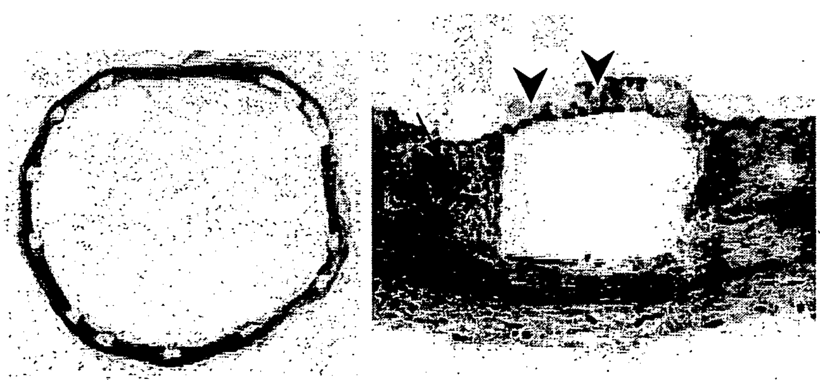


FIG. 38

FIG. 39



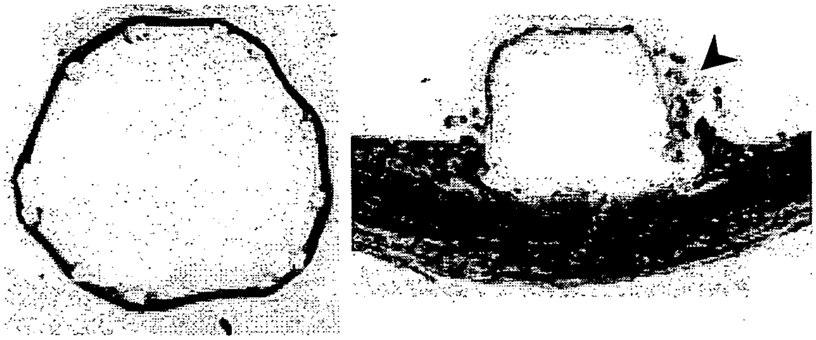


FIG. 40

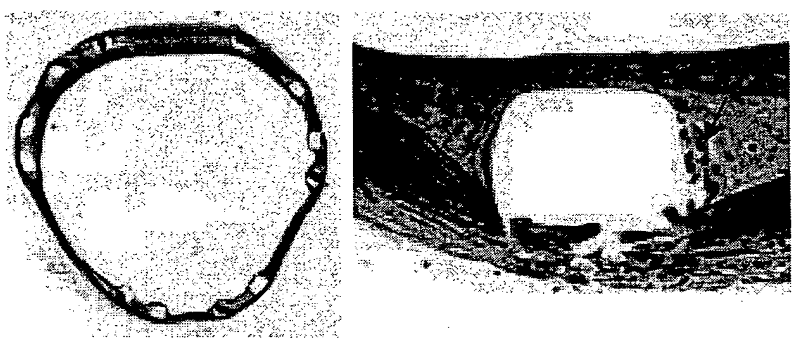


FIG. 41

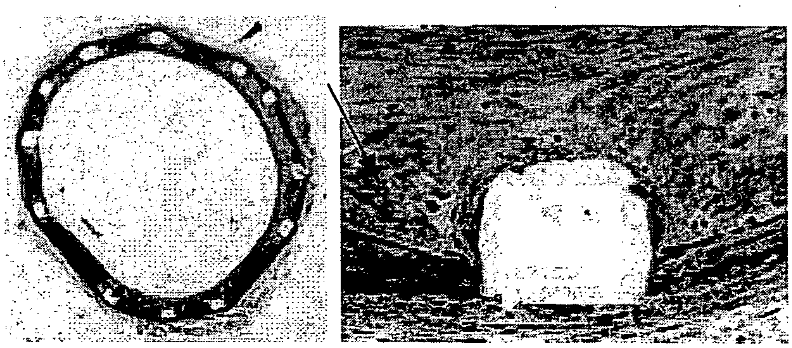


FIG. 42

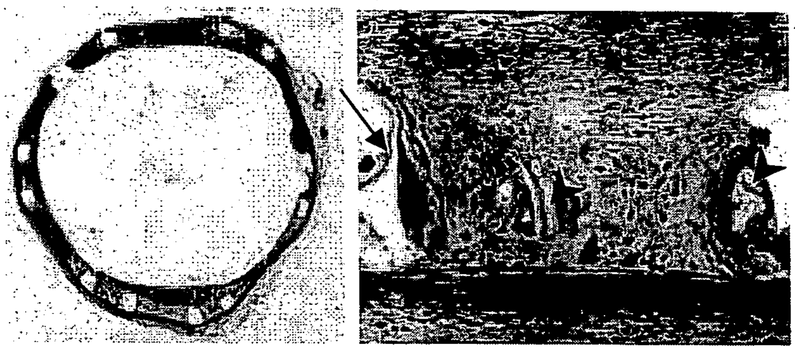


FIG. 43

uncrimped/unexpanded

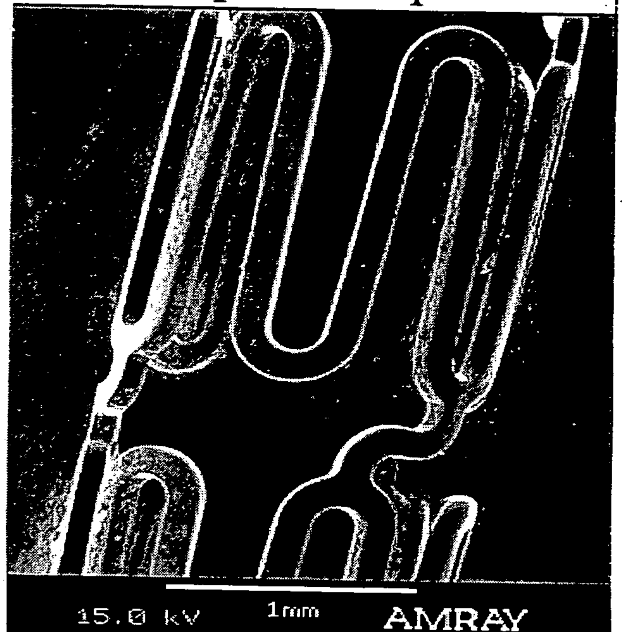


FIG. 44a

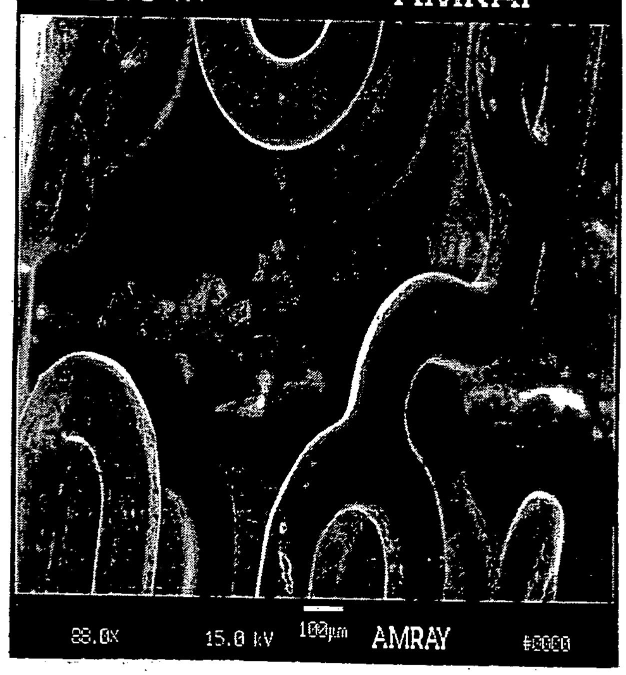


FIG. 44b

uncrimped/unexpanded

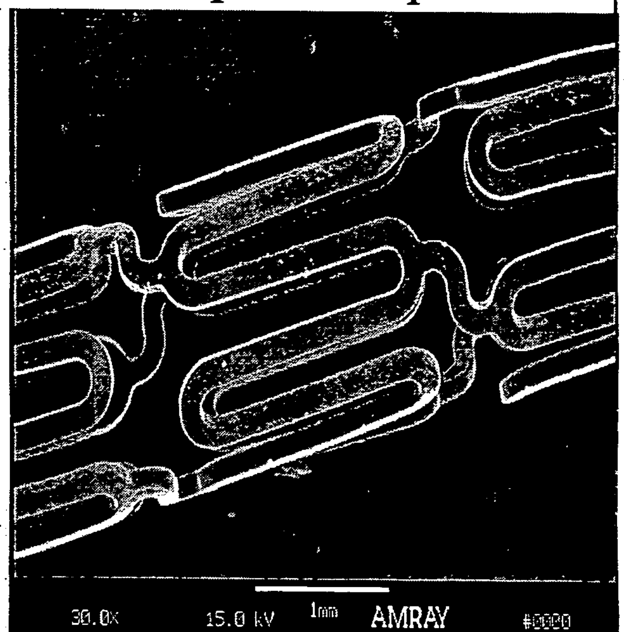


FIG. 45a

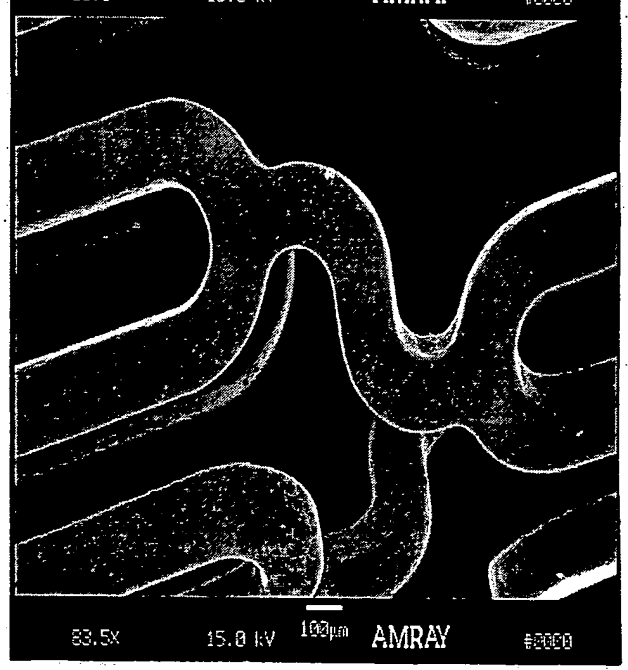


FIG. 45b

uncrimped/unexpanded

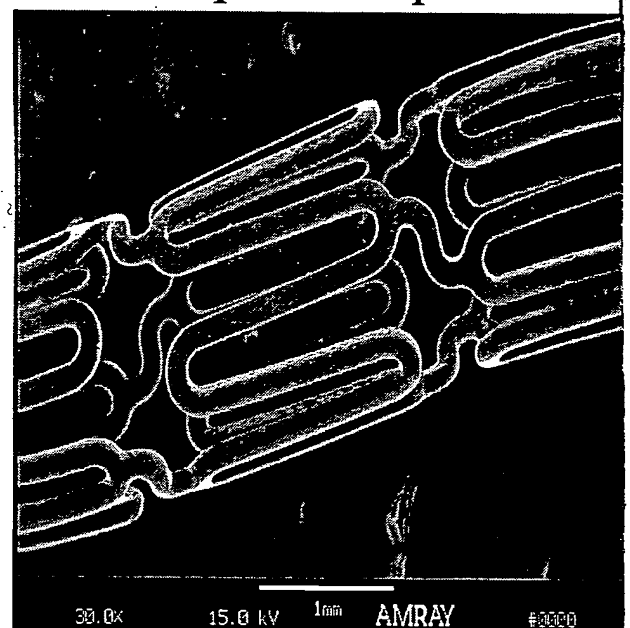


FIG. 46a

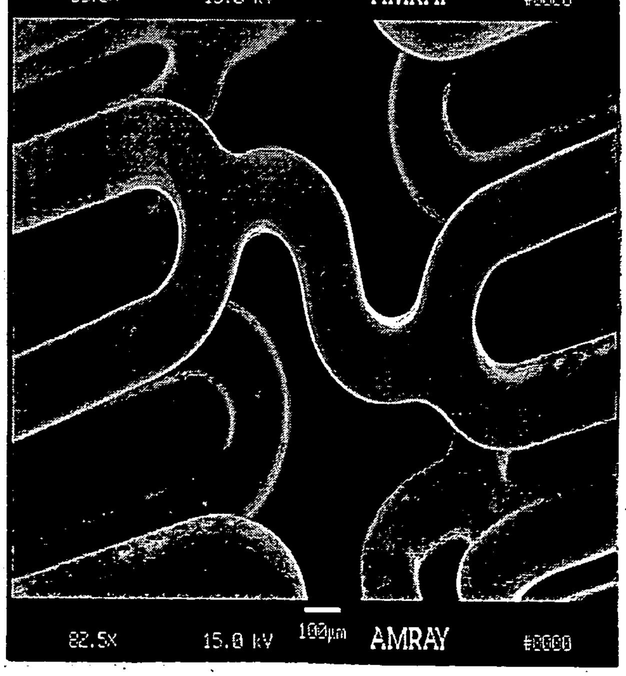


FIG. 46b